ORIGINAL ARTICLE

The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi

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Aim: To compare presentation, progress, and outcome of acute bacterial meningitis in HIV seropositive and seronegative children.

Methods: A double blind randomised placebo controlled study of the use of dexamethasone as adjuvant therapy in acute bacterial meningitis, in children aged 2 months to 13 years, was carried out from July 1997 to March 2001. A total of 598 children were enrolled, of whom 459 were tested for HIV serostatus.

Results: Of the 459 children, 34% were HIV seropositive. Their presentation was similar to HIV seronegative children but more were shocked on arrival at hospital (33/157 *v* 12/302), and more had a focus of infection (85/157 *v* 57/302). HIV positive children had a higher incidence of *Streptococcus pneumoniae* infections (52% *v* 32%). Sixty four cases relapsed; 67% were in HIV positive patients. The mortality in HIV positive children was 65% compared with 36% in HIV negative children. The number of survivors in each group was similar. Hearing loss was more common in HIV negative than HIV positive children (66.3% *v* 47.2%). Steroid therapy had no influence on meningitis in HIV positive children, but the mortality in HIV negative children was 61% in children given steroids, and 39% in those who did not receive steroids.

Conclusion: HIV seropositive children who develop bacterial meningitis have a high mortality and are prone to recurrent disease. There is an urgent need to prevent both primary and recurrent infections.

Bacterial meningitis is ten times more common in children in developing than in developed countries.[1] In resource poor countries the case fatality rate is high (12–50%) compared with richer countries (<5%), and a third of all survivors are left with sequelae.[1–6]

In many resource poor countries the prevalence of human immunodeficiency virus type 1 (HIV) infection among children is increasing. HIV infection makes a child more prone to invasive bacterial infections, including bacterial meningitis.

We wished to know whether the presentation of bacterial meningitis, the course of the illness, or the outcome were different in HIV infected and uninfected children.

The Queen Elizabeth Central Hospital (QECH) is an 1100 bedded government referral and teaching hospital in Blantyre, Malawi. The paediatric department has 250 beds with up to 310 inpatients. In the paediatric accident and emergency unit more than 90 000 children are seen each year, of whom 12 000 are admitted. A prevalence study of HIV infection rates for inpatients was carried out over a two week period in the malaria season of 2000. Children below 18 months of age who were seropositive had HIV PCR tests done to confirm their status. An overall HIV infection rate of 18.3% was found for all admissions regardless of diagnosis.[7] In an audit of children admitted to the nutrition unit it was found that 62% of marasmic children and 21.7% of those with kwashiokor were HIV infected.[8] On the tuberculosis (TB) ward the seroprevalence was 70.6% in those suspected of TB and who agreed to be tested. In confirmed or ''probable'' cases of pulmonary tuberculosis HIV infection rates were 57.8%.[9]

Gastroenteritis, pneumonia, TB, and malaria are the most common causes of hospital admissions. In a previous study 2.7% of all admissions were due to bacterial meningitis.[5] Malnutrition plays a significant underlying role in all the problems of children requiring admission.

Children with HIV related illnesses are treated appropriately, but anti-retroviral medicines are not available. Infants and children are not routinely tested for HIV serological status.

METHODS

From July 1997 to March 2001 we conducted a double blind randomised placebo controlled study of the role of dexamethasone as an adjuvant therapy in the treatment of bacterial meningitis in children aged 2 months to 13 years.[6] Meningitis was defined as the presence of ⩾100 white cells per mm^3, predominantly granulocytes, in an admission sample of cerebrospinal fluid (CSF), *or* a positive Gram stain showing bacteria in CSF, *or* the culture of bacteria from CSF. Children who had received parenteral broad spectrum antibiotics up to 24 hours prior to admission were excluded from the study.

Procedure

All study children had a complete history taken and were fully examined and weighed. A lumbar puncture was done and if meningitis was suspected by the naked eye appearance of the CSF sample, an intravenous line was established. Blood samples were taken for full blood count, malaria parasites (thick film), plasma glucose and electrolytes, and blood culture. Blood was not cultured if the CSF report was already available and confirmed the presence of bacteria on Gram stain. Sera and red cell pellets were stored. Patients were randomised to receive either dexamethasone (0.4 mg/kg intravenously 12 hourly for 48 hours) or placebo 5–10

minutes before antibiotic doses for the first two days of a 10 day course of antibiotics.

Randomisation

Randomisation was done in blocks of 10, with the randomisation code held by the clinical monitor in a sealed envelope. Vials of dexamethasone or placebo were identical, labelled with only the study number, and contained 1 ml of clear liquid. The placebo vials contained water for injection, the active vials contained 5 mg of dexamethasone. Neither those who gave clinical care to the patients nor the patients' guardians were aware of the contents of the vials. All managements, outcome assessments, and data analysis were done without breaking the code.

Chloramphenicol (100 mg/kg/24 h) and benzylpenicillin (200 000 iu/kg/24 h) were the first-line antibiotics given. When CSF cultures and sensitivities were known, antibiotic therapy was continued or altered accordingly. During the study 39 children with Gram negative bacilli seen on the Gram stain of the CSF specimen were started directly on ceftriaxone as there was known to be increasing resistance of some *Haemophilus influenzae* type b to chloramphenicol. An ultrasound scan of the head was done if the child's fontanelle was still patent, either for clinical indications, or before discharge from hospital. A full physical examination including head circumference measurement, neurological function, and hearing and visual assessments were done prior to discharge from hospital and at 1 and 6 months after discharge. If the child had made a complete recovery from meningitis, was old enough to be properly assessed, and lived far from the hospital, follow up was not carried out. If the child had sequelae that required further management beyond 6 months, follow up was continued. Of the 348 survivors, 36 (10%) were not reviewed, 73 (21%) were seen 1 month, 33 (9%) 1–6 months, and 242 (69.5%) ⩾6 months post-discharge from hospital.

The results and detailed methodology of this study have been previously reported.[6] HIV testing was undertaken with parental agreement and accompanied by pre- and post-test counselling. Ethical permission for the study was given by the National Health Sciences Research Committee.

Laboratory methods

CSF samples were examined microscopically for total cell count and white cell differential count. A Gram stain was done on all samples that were cloudy or contained more than 8 WBC/mm^3. After centrifugation, the deposits were cultured on sheep blood agar (SBA) and haemophilus test medium (HTM), both incubated in a candle jar at 37℃ for 48 hours; 5 ml brain heart infusion broth with 1% Vitox was added to the remaining deposit for enrichment culture. This broth was incubated for 48 hours, and then the centrifuged deposit was cultured on SBA and HTM plates which were incubated for 48 hours as for the direct cultures.

Blood cultures were done using a manual method; a maximum blood volume of 2 ml was added to a single blood culture bottle (20 ml brain heart infusion broth containing sodium polyanethol sulphonate, E&O Laboratories, UK). Bottles were incubated overnight at 37℃ before venting. Cultures were examined macroscopically every day, followed by Gram staining if turbid or haemolysed. Subcultures and direct susceptibility testing were performed as directed by the Gram stain findings. Routine subcultures on sheep blood agar were performed for all bottles after 18–24 hours, 36–48 hours, and 7 days. All plates were incubated in a candle jar, and examined after 24 and 48 hours incubation.

Isolates were identified according to standard techniques,[10] including optochin susceptibility, seroagglutination for *Haemophilus influenzae* type b and salmonellae, and biochemical tests. Antibiotic susceptibilities were determined by disc diffusion on Mueller-Hinton agar, interpreted using the NCCLS guidelines.[11] For pneumococci, penicillin susceptibility was assessed with a screening technique using a 1 μg oxacillin disc. Minimum inhibitory concentrations were not performed for any isolate.

HIV tests

Serum samples were tested by at least two of the following tests: Serodia-HIV particle agglutination (Fujirebio Inc., Mast Diagnostics, UK), HIVSPOT (Genelabs Diagnostics, Singapore), Determine-HIV (Abbott Laboratories, USA), Capillus-HIV (Cambridge Diagnostics, Ireland). Discordant tests were confirmed either by a third test or an in-house HIV PCR. Nested PCR was used for detection of the long terminal repeat of HIV. The primary PCR was performed using proviral oligonucleotides 5′-ACCAGRTYTGAGCCTGGGAGCT and 5′-CCTGTTCGGCGCCACTGCTAGAGATTTT and using 5′-TGAG CCTGGGAGCTCTCTGGCT and 5′-CTGAGGGATCTCTAGDYA CCAGAGT for the secondary reaction. Both reactions were run for 35 cycles of 94℃ for 30 seconds, 46℃ for 30 seconds, 72℃ for 30 seconds, with a final extension of 72℃ for 10 minutes. Children below 18 months of age with a positive antibody test were confirmed with the HIV PCR test.

Data

Data were entered in a Microsoft Excel file. This was double checked and analysed with Epi Info.6.

All 2×2 tables were analysed using Yates's correction of Pearson's χ^2 statistic. Time to clearance of fever was analysed using the Mann-Whitney U test. Models were selected in multiple logistic regression using a forward selection procedure. Significance tests were performed using likelihood ratio tests. A natural log transformation was applied to age (months). Odds ratios (OR) with 95% confidence intervals (CI) were estimated using the data for all patients with the selected variables, using the estimated standard errors.

RESULTS

Presentation

A total of 598 cases of meningitis were enrolled, of whom 459 were tested for HIV status. Of the 139 not tested, 100 were enrolled before permission was granted by the ethics committee to request the tests, 33 were inadvertently not asked or tested, five guardians refused permission for the test, and in one case no appropriate guardian was available to give permission. A total of 157 (34%) of the 459 tested were HIV infected. These children did not differ in age from the HIV uninfected children (table 1). The HIV infected children more commonly had generalised signs of HIV infection such as lymphadenopathy, hepatosplenomegaly, and a lower weight for age. On presentation the HIV infected and uninfected children had similar lengths of history of fever. Similar numbers in each group were admitted with a history of seizures or with a low coma score. The HIV infected patients were more likely to be in shock, or have a focus of infection (85/157 *v* 57/302, p<0.0001; OR 5.07, 95% CI 3.2 to 7.96) (table 1). Thirty nine of the 85 (46%) infections in HIV infected children were due to *Streptococcus pneumoniae* compared to 11 of 57 (19%) in uninfected children (p = 0.002; RR 2.38, 95% CI 1.33 to 4.24). In the HIV infected children *S pneumoniae* infections mainly affected ears (n = 20/32) or the chest (n = 10/18). In the uninfected children 6 of 24 ear infections, and 2 of 8 chest infections were due to *S pneumoniae*. Foci of infection due to *Haemophilus influenzae* were found in both groups of children (10/85 HIV infected *v* 12/52 uninfected, p = 0.1).

Table 1 Findings on presentation of bacterial meningitis in different HIV status groups

HIV seropositivity	HIV+ (%)	HIV− (%)	Significant differences between HIV+ and HIV− groups
Number of children	157	302	
Median age (months) [range]	12 [2–168]	12 [2–164]	
Male:female	47:53	60:40	
Median % wt for age [range]	73 [39–126]	81 [39–123]	
Median fever (days) [range]	3 [0–60]	3 [0–30]	
⩽2 days fever	76 (48)	114 (38)	
History of seizures	94 (60)	132 (44)	p=001, OR 1.92 (1.27 to 2.90)
Focal fits (%of fits)	19(12)	29(22)	p=0.5, OR 1.3 (0.67 to 2.49)
Not sucking	90 (57)	128 (42)	p=0.03
Prior antibiotics	73 (46)	101 (33)	
Ear infection	32 (20)	24 (8)	p=0.0002, OR 2.97 (1.61 to 5.48)
Focus of infection	85 (54)	57 (19)	p=0.0001, OR 5.07 (3.2 to 7.96)
Coma score ⩽2	67 (43)	111 (37)	p=0.26
Skin rash	18 (11)	11 (4)	p=0.02, OR 3.43 (1.49 to 7.99)
Generalised LN++	32 (20)	12 (4)	p<0.00001, OR 6.19 (2.95 to 13.18)
Hepatomegaly	65 (41)	51 (17)	p<0.00001, OR 3.48 (2.19 to 5.52)
Splenomegaly	43 (27)	59 (19.5)	p=0.07, OR 1.4 (1 to 1.97)
Shock	33 (21)	12 (4)	p<0.00001, OR 6.43 (3.08 to 13.69)
Mean blood glucose (mmol/l) [range]	5.6 [0–37]	5.9 [0–13]	
Median temp (℃) [range]	38 [34–41]	38.4 [35–40.8]	
Median haematocrit (mg/l) [range]	290 [160–450]	300 [70–500]	
Malaria parasites +	(13.4)	(16.4)	
H influenzae	32 (20)	98 (32)	p=0.009, OR 0.53 (0.33 to 0.86)
S pneumoniae	92 (58)	98 (32)	p<0.0001, OR 2.95 (1.94 to 4.48)
N meningitidis	4 (2)	32 (10.5)	p=0.004, OR 0.22 (0.06 to 0.67)
Salmonellae spp.	10 (6)	14 (5)	p=0.56, OR 1.4 (0.56 to 3.45)
No growth	14 (9)	50 (16.5)	p=0.035, OR 0.49 (0.25 to 0.96)
Other	5 (3)	10 (3)	p=0.8

Table 2 Progress in hospital in different HIV serostatus groups

HIV seropositivity	HIV+	HIV−	Differences between HIV+ and HIV−
Number of children	157	302	
Median time (h) for temp ⩽37°C ⩾24 h [range]	33 [6–264]	24 [1–456]	
Number requiring anticonvulsant therapy	74 (47%)	119 (39%)	p=0.135
Ultrasound scan of head done	28	82	
Abnormal findings on ultrasound	13 (46%)	34 (41%)	p=0.8
Number requiring 2nd line antibiotic therapy	43 (27%)	114 (38%)	p=0.03
Subdural/abscess tapped*	3 (2%)	6 (2%)	p=0.6
Blood transfusions†	3 (2%)	6 (2%)	p=0.6

*Includes two brain abscesses (one ventricular tap (*S pneumoniae*) and one necrotic post-infarct abscess (*E coli*).
†Transfusions given on admission or during stay in hospital.

Causes of meningitis

The same bacteria caused meningitis in the two groups of children but in HIV infected children the proportion of cases caused by *Streptococcus pneumoniae* was significantly greater than in the uninfected group (table 1).

Progress in hospital

HIV infected children who were febrile took longer to become afebrile than uninfected children. In other respects the illness progressed similarly in both patient groups. A similar number required anticonvulsants, blood transfusions, or a change in antibiotic therapy. Abnormal results from ultrasound scans of the brain were also similar (table 2).

Recurrence of meningitis

Of the 598 episodes of meningitis, 64 were recurrent. Forty four (68%) recurrences were in HIV infected children, 13 (20%) in HIV uninfected children, and eight (12.5%) in children in whom HIV was not tested. The relative risk of recurrence in HIV infected children (44/157) compared with HIV uninfected children (13/302) was 6.4 (3.5 to 11.5) (p<0.00001).

Twenty eight (44%) cases were due to *S pneumoniae*, and 17 (26.5%) were due to salmonellae species (table 3). In the cases due to *S pneumoniae*, 18 (64.2%) were HIV positive, five

Table 3 Recurrent meningitis

Cause	Serostatus		Total
	HIV+	HIV−	
Streptococcus pneumoniae	18	5	23
Salmonella spp.	12	5	17
Unrecorded*	7	0	7
Haemophilus influenzae b	2	2	4
No growth	3	0	3
Neisseria meningitidis	0	1	1
E coli	1	0	1
Total	43	13	56

*No results available; episode of meningitis managed elsewhere.

were negative, and five were not tested for HIV serology. The relative risk of recurrence for pneumococcal meningitis in HIV positive children (18/93) compared with HIV negative children (5/99) was 3.8 (1.5 to 9.9) ($p<0.005$).

Seventy per cent of the cases caused by a *Salmonella* sp., were HIV infected (table 3). The recurrences after the first episode of *Salmonella* sp. meningitis were from 7 days to 3 months. Recurrent *S pneumoniae* meningitis occurred from 2 weeks to 2 years after the first episode; only two episodes occurred <2 months after the first infection. In two cases of *S pneumoniae* meningitis the recurrence was due to another bacterium (one *E coli* and one *H influenzae*). All the Salmonella sp. infections had recurrences of the same bacteria. The time between infections was unaffected by the HIV serostatus of the child.

Recurrent episodes of infection were not caused by bacteria more resistant to chloramphenicol and/or penicillin than with the first infection. In two recurrent cases, one each of *S pneumoniae* and *H influenzae* type b, the bacteria had acquired chloramphenicol resistance that was apparent on in vitro testing of the isolate from the recurrent infection. Of these two cases one child was HIV infected and one was uninfected.

Outcome

The outcome was significantly worse in the children who were HIV infected; in the study period, 102 of 157 (65%) died compared with 109 of 302 (36%) HIV uninfected children ($p<0.00001$; RR 1.8 (1.49 to 2.17)). In HIV infected children, 94 of 157 (59.8%) deaths were directly attributable to meningitis compared with 103 of 302 (34%) in uninfected patients ($p<0.0000002$; RR 1.76 (1.43 to 2.15)). The HIV infected children who died were more malnourished than the HIV infected survivors ($p = 0.015$). A logistic regression model shows that for a 10% reduction on weight for age (WFA) the odds of death are estimated to be increased by a factor of 1.275 (95% CI 104 to 155). Among survivors the overall likelihood of having sequelae was unaffected by HIV status (30/55 HIV+ *v* 88/193 HIV–, $p = 0.83$). Neurological sequelae were found in 21/55 (38%) HIV infected survivors versus 55/107(51.4%) in HIV uninfected surviving children ($p = 0.15$). The pattern of hearing loss in the two groups of survivors was similar but was less common in HIV infected than uninfected survivors (26/55 (47.2%) *v* 71/107 (66.3%), $p = 0.029$). Hearing loss was equally profound in both groups. The types of neurological sequelae were similar in each group except that hydrocephalus was found in 5/107 HIV uninfected survivors and in no HIV infected survivors (table 4).

The role of steroids and HIV status on outcome

Outcome with full recovery, death, or residual sequelae was uninfluenced by the use of steroids as adjuvant therapy in HIV infected children. In HIV infected patients receiving adjuvant dexamethasone therapy the case fatality rate was 52% (38/73) compared with 39% (62/159) in HIV uninfected patients($p = 0.08$; RR 1.33 (1.0 to 1.79)) (table 5).

Laboratory results in HIV infected and uninfected patients

The blood glucose level on admission and the number of children with malaria parasitaemia was similar in each group. The peripheral white cell count was similar with a median of 12 (range 1–70)$\times 10^6$/mm^3 in HIV uninfected children and 10.8 (range 1–70)$\times 10^6$/mm^3 in infected children. The white cell count in CSF varied widely but the median count in the infected group was 1925 (range 0–>100 000)/mm^3 and in the uninfected group was 840 (range 0–100 000)/mm^3 ($p = 0.83$). The total peripheral lympho cyte count was not different in the HIV positive (mean lymphocyte count 33 642/mm^3) and HIV negative groups (mean lymphocyte count 36 944/mm^3). The total lymphocyte count was not significantly different in the group of HIV infected children who died and the group that survived ($p = 0.51$).

Bacterial resistance to first line antibiotics

There was no overall difference in bacterial resistance on in vitro testing by HIV status, with the exception of pneumococci from HIV infected patients, of which fewer were resistant to chloramphenicol than those in HIV uninfected patients (3% *v* 16%, $p = 0.006$) (table 6).

Fifteen per cent of *H influenzae* infections (15/99) and 13% (13/97) of *S pneumoniae* infections in HIV negative children were fully sensitive to the antibiotics against which routine testing is carried out (penicillin, ampicillin, chloramphenicol, gentamicin, cotrimoxazole, cefaclor, and erythromycin). In HIV infected children, 12.5% (4/32) of *H influenzae* infections and 4.4% (4/89) of *S pneumoniae* infections were fully sensitive to the antibiotics against which they were screened (table 6).

Of the children who had received known prior antibiotics, 31 of 73 (42%) HIV infected children had received penicillin compared with 59 of 104 (58%) uninfected children ($p = 0.04$). Cotrimoxazole had been given to 23 (31.5%) of the HIV positive versus 16 (16%) of the seronegative group ($p = 0.03$). Very few had received chloramphenicol (10/73 *v* 14/101) ($p = 0.9$).

DISCUSSION

In this study HIV infected children with bacterial meningitis were more likely to die than uninfected children (59.8% *v* 34%, $p<0.00001$). Fifteen per cent (24/157) of HIV infected patients made a full recovery compared with 91/302 (30%) in the uninfected group ($p<0.001$). Children who survived with sequelae had the same types of problems regardless of HIV status. Hearing loss was similar but less common in the HIV infected group. Steroids marginally increased the case fatality rate in HIV uninfected children ($p = 0.08$) but not the incidence of sequelae in either group. Recurrence could not be attributed to drug resistance. Sensitivity patterns of bacteria were similar between groups for the first and for the recurrent infections. We were unable to distinguish between recrudescent infections and new infections (recurrences occurred between 2 weeks and 18 months after the first infection), and it is possible that the greater recurrence rate in the HIV infected group simply reflects a greater susceptibility to invasive bacterial disease. More HIV infected children presented with foci of infection (54% *v* 19%, $p<0.0001$) than uninfected patients and more of the foci were due to *S pneumoniae* (46% *v* 19%). More children were in shock (21% *v* 4%) on arrival to hospital, but in other ways they were no sicker on arrival than HIV uninfected children.

HIV infected children took longer to become afebrile, but the number who needed anticonvulsants, second line antibiotics, or blood transfusions did not differ from uninfected patients. The total lymphocyte count did not predict outcome in HIV seropositive children. The total lymphocyte count has been used as a surrogate marker for CD4 count. This has been shown to be useful (though not very specific or sensitive) as an indicator for starting HAART therapy in HIV positive adults.[12 13] It is yet to be seen if this is true in childhood and in a endemic malarial area where white cell counts are depressed by malarial infections. Our children had a severe infection which would acutely affect the peripheral white cell count and reduce the predictive value of a total lymphocyte count.

Poor nutrition is associated with a poor outcome from meningitis, and a low weight for age was associated with a

Table 4 Outcome by different causative agents and HIV serostatus

	Overall (n = 459)		Causative agent (%)											
			S pneumoniae (n = 192)		*H influenzae* (n = 131)		*N meningitidis* (n = 36)		*Salmonella* spp (n = 24)		No growth (n = 64)		Other (n = 13)	
	HIV+	HIV−	HIV+	HIV−	HIV+	HIV−	HIV+	HIV−	HIV+	HIV−	HIV+	HIV−	HIV+	HIV−
Number of children	157	302	93	99	32	99	4	32	10	14	14	50	4	9
Died in hospital	88	89	48	39	21	26	0	1	8	7	9	12	1	4
Died after discharge of meningitis problem	6	14	4	4	0	5	2	0	0	2	1	2	1	0
Died after discharge of non-meningitis illness	8	6	4	3	0	1	0	0	1	0	0	1	1	0
Survivors with full recovery*	27 (17)	92 (30)	18	17	5	30	1	22	0	0	3	21	1	2
Total with sequelae* (%)	30 (19)	88 (29)	17	34	6	27	3	8	2	5	1	11	1	3
All neuro problems†	21	55	7	16	5	17		3	1	2	0	9	2	1
All with hearing loss	26	71	18	27	1	21	3	9	3	4	3	8	0	2
Hearing normal	24	103	14	21	8	35	1	20	0	1	1	23	0	3
Bilateral loss	12	35	8	16	1	7	1	2	1	3	1	5	0	2
Bilateral reduction	6	7	4	3	0	2	1	1	1	0	0	1	0	0
Unilateral loss	1	14	1	8	0	2	0	3	0	1	0	0	0	0
Unilateral reduction	1	5	0	0	0	3	1	2	0	0	0	0	0	0
Conductive loss	6	10	5	0	0	7	0	1	0	0	1	2	0	0
Inconclusive tests*	10	19	5	3	2	11	0	1	0	1	1	3	2	0
Not tested	3	14	2	5	0	3	0	1	0	0	1	4	0	1

*Includes 8 too young for testing and seen when oto-evoked emission test not available,15 neurologically damaged and seen when oto-evoked emission test not available, 1 child uncooperative,1 history and findings incompatible,1 unknown.
†Excludes hearing problems.

Table 5 Role of HIV status on outcome in steroid treated and placebo groups

	HIV status	Total (%)	Steroids	No steroids
Total	+	157	73 (46)	84 (53.5)
Alive and well	+	27 (17)	13 (48)	14 (50)
Died	+	94 (60)	38 (52)	56 (67), p = 0.08 (RR 0.6 to 1.02)
Sequelae	+	30 (19)	18 (60)	12 (40)
?	+	6	4	2
Total	−	302	159 (53)	143 (47)
Alive and well	−	92 (30)	43 (27)	49 (59)
Died	−	103 (34)	62 (61)	40 (39), p = 0.05 (RR 0.99 to 2.75)*
Sequelae	−	88 (29)	39 (44)	49 (56)
?		20	15	5

Died: only includes meningitis related deaths.
*No other significant differences found between the groups.

Table 6 Pattern of bacterial resistance to first line antibiotics used in meningitis

	Resistance to antibiotics (%)		
	Serostatus	Total chloramphenicol	Penicillin
HIV+	139	14 (10)	40 (29)
HIV−	247	40 (16)	86 (35)
HIV + *H influenzae*	32	5 (16)	9 (28)
HIV − *H influenzae*	99	17 (17)	55 (55.5)
HIV + *S pneumoniae*	89	3 (3.3)*	19 (21)
HIV − *S pneumoniae*	97	16 (16)*	14 (14)
HIV + *Salmonella* sp.	10	4 (40)	10 (100)†
HIV − *Salmonella* sp.	15	3 (20)	13 (89)†

*p = 0.006, †p = 0.05; no other significant differences.

poor outcome our study.[5 6 14] The HIV infected patients who died were significantly more wasted than the children who survived (p = 0.015).

In a literature review of bacterial meningitis in children who are HIV infected in developing countries, only a few reports focused on this problem. Madhi *et al* in South Africa reviewed their admissions for bacterial meningitis over a two year period (March 1997 to February 1999) and found that 62 (42%) of the 147 cases were HIV infected. The mortality was 30.6% compared with 11.8% in HIV uninfected children. The causes of bacterial meningitis were *S pneumoniae* in 74.2% of HIV infected children versus 12.9% in HIV uninfected children. *H influenzae* caused meningitis in 42.3% of HIV uninfected children versus 29.4% in HIV infected children.[14] The same group of researchers reported that in a study of pneumoccocal infections it was noted that *S pneumoniae* meningitis was significantly more common in HIV infected children than uninfected children (p = 0.003) and 64% of systemic pneumococcal infections in patients below the age of 12 years were in HIV infected patients.[15] In that study, unlike in ours, shock was found to be more common in HIV uninfected children with systemic *S pneumoniae* infections than in HIV infected children (p = 0.0003). This group report that systemic pneumococcal infections are 40 times more likely in HIV infected than uninfected patients.[16] In post-mortem examinations carried out on HIV infected children in Cote D'Ivoire, bacterial meningitis was no more common in HIV infected than HIV uninfected children.[17] Several studies, which include and were predominantly about adults, note the rise in meningitis incidence and the predominance of cryptococcal meningitis, TB meningitis, and lymphocytic meningitis in AIDS patients.[18–20] In Soweto bacterial meningitis caused 22.5% of meningitis in HIV positive (adult) patients.[19] In Harare pyogenic meningitis accounted for 16% of cases of meningitis, of whom 81% were HIV positive.[18] During the time of this study we had one case of childhood cryptococcal meningitis and six cases of confirmed TB meningitis.

In South Africa Madhi *et al* reported a rise in penicillin resistance of *S pneumoniae* infections in HIV infected patients compared with uninfected patients (46% *v* 28%, p = 0.009). Cotrimoxazole resistance was 44.5% in HIV infected and 19% in HIV uninfected patients.[15] We found 21% resistance to penicillin in HIV infected patients and 14% resistance in uninfected patients with *S pneumoniae* meningitis. Cotrimoxazole resistance is high (>80%) in both groups of patients, and only 4.4% of all infections in HIV infected children were fully sensitive to routine antibiotic screening (Lorna Wilson; personal communication). However, chloramphenicol resistance was less in HIV infected patients than uninfected patients (p = 0.006) (table 6).

Children who are HIV infected are prone to develop systemic bacterial infections, including meningitis, and have a high mortality. In our experience, if they recover from meningitis the likelihood of a recurrent infection is high. There is clearly a need to prevent both primary and recurrent infections. We do not know if prophylactic antibiotics would be helpful, and if so, which antibiotic to choose as cotrimoxazole resistance is widespread in our setting. After one episode of bacterial meningitis, should all HIV infected children be given monthly injections of benzathine penicillin to try to prevent recurrence? The use of conjugate vaccines against *H influenzae* type b and *S pneumoniae* looks more promising and needs to be evaluated in HIV infected children as soon as possible.[21–25]

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